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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

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In re Application of :

Wolfgang R. STREBER et al. :

Serial No.: 07/322,604 : Group Art Unit: 1812

Filed: March 10, 1989 : Examiner: J. Ulm

For: MICROORGANISMS AND PLASMIDS FOR 2,4-DICHLORO-PHENOXYACETIC ACID (2,4-D) MONOOXYGENASE FORMATION AND PROCESS FOR THE PRODUCTION OF THESE PLASMIDS AND STRAINS

94-0224

BRIEF ON APPEAL

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

Further to the Notice of Appeal filed May 26, 1992, herewith are three copies of appellants' Brief on Appeal. The Commissioner is hereby authorized to charge the statutory fee of $260 and $110 for a one-month extension of time to counsel's Deposit Account No. 13-3402 and to debit or credit Deposit Account No. 13-3402 for any under- or overpayment of these fees. Two copies of this page are attached.

Status of the Claims

Claims 17, 18, 23, 32, 33, 35, 42, 43, and 45-53 are on appeal. It is noted that claim 23, which is still pending in the application, was omitted from the Advisory Action.

Status of the Amendments

All amendments have been entered.

Summary of the Invention

The invention is directed to a recombinant gene, comprising a DNA sequence encoding a polypeptide having the biological activity of 2,4-D monooxygenase which is capable of

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being expressed in a plant, operably linked to a heterologous promoter capable of promoting the expression in a plant of a structural gene operably linked thereto (page 4, lines 24-31); a recombinant vector comprising said recombinant gene (page 4, lines 24-31); bacterial strains transformed with said vectors (page 4, lines 32-36); transgenic plants comprising said recombinant genes (page 5, lines 1-4) and methods of preparing polypeptides comprising expressing said genes (page 4, lines 32-36).

Issues on Appeal

The issues on appeal are:

1. whether the rejection of claims 23, 32, 33, 35, 42, 43, 45, 48, and 51-53 under 35 U.S.C. §112, first paragraph, is proper;

2. whether the rejection of claims 18, 35, and 46 under 35 U.S.C. §112, second paragraph, is proper; and

3. whether the rejection of claims 17, 18, 32, 35, 42, 43, and 45-53 under 35 U.S.C. §103 as being unpatentable over Amy et al., Beguin et al. and Carey et al. in view of Comai et al. is proper.

Grouping of Claims

All claims stand or fall together.

Arguments

The rejection of claims 23, 32, 33, 35, 42, 43, 45, 48, and 51-53 under 35 U.S.C. §112, first paragraph

Appellants respectfully submit that the rejected claims are fully supported by the specification. The specification provides, inter alia, screening methods which would enable a skilled worker, without undue experimentation, to isolate clones containing expression vectors comprising DNA sequences from **any** organism, wherein the clones contain functionally inserted DNA sequences coding for the enzyme 2,4-D monooxygenase, so that the enzyme allows for the growth of the 2,4-D-expressing clones under conditions which preclude

the growth of non-expressing clones. See, e.g., page 5, lines 5-17. Thus, the hybridizability of additional sequences with the disclosed sequence is not the only means of selection, and the functional language in the claims is fully supported in the specification.

Furthermore, this screening technique, or a variation modifiable by the skilled worker, could be used to isolate DNA sequences encoding **any** 2,4-D monooxygenase gene which is sufficiently expressible to permit growth of expressing clones under conditions where 2,4-D is the only carbon source, not only those from organisms able to use 2,4-D as an ancillary carbon source, since the cloning technique provides vectors free of their usual controls. Thus, even if a particular species containing a 2,4-D monooxygenase gene which could only use 2,4-D as an ancillary carbon source could not support growth using 2,4-D as a sole carbon source, a screening technique according to the present invention which would enable constitutive production of 2,4-D monooxygenase in the cloned cell could still identify the gene.

However, and in any case, according to In re Marzocchi, 169 U.S.P.Q. 367 (C.C.P.A. 1971):

> The first paragraph of §112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.

and

> [T]he claims are to be read in light of the specification, and a specification disclosure which contains a teaching of the manner of using the invention in terms corresponding in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of §112, *unless* there is reason to doubt the objective truth of statements therein.

The Examiner has merely suggested, without providing anything other than his speculation as basis for the allegation, i.e., without any evidence or sound scientific reasoning, that other sequences falling within the claimed genus might exist which

would not be enabled by the specification. In addition to the fact that this allegation has been adequately rebutted above, this is not a proper basis for a rejection under §112, first paragraph, and withdrawal of the rejection is respectfully requested.

The rejection of claims 18, 35, and 46 under 35 U.S.C. §112, second paragraph

The rejection based upon improper dependency of claims 18 and 35 was rendered moot by entry of the amendment.

Claim 46 was amended to include functional language **explicitly** specifying that sequences hybridizable with the specified sequences code for polypeptides having the biological activity of 2,4-D monooxygenase. This inherently implies a size limitation. One of ordinary skill in the art would be able to routinely determine suitable hybridization conditions from the specification, e.g., by reference to the Maniatis text incorporated by reference in the specification, to identify hybridizable sequences likely to retain the biological activity of 2,4-D monooxygenase. The rejection is, therefore, respectfully submitted to be improper.

The rejection of claims 17, 18, 32, 35, 42, 43, and 45-53 under 35 U.S.C. §103 as being unpatentable over Amy et al., Beguin et al. and Carey et al. in view of Comai et al.

The references:

Amy et al. merely isolated a 2,4-D monooxygenase gene, from a different organism, but did not sequence the gene or provide any other teaching which would lead a skilled worker to determine how to express the procaryotic monooxygenase gene is plant cells.

Beguin et al. disclose subcloning and sequencing techniques.

Carey et al. teaches construction and use of particular heterologous promoters for regulation of exogenous genes in bacteria using a bacterial promoter, and not in plants.

Comai et al. discloses the insertion of a very different bacterial enzyme having an endogenous homolog into a plant (in order to provide extra copies of the gene to make more of the protein product which protects against a different herbicide), as compared with the insertion of a completely exogenous gene (foreign to the plant, having no homolog therein) of the present invention.

Argument

Even if the DNA sequence of the gene cloned by Amy et al. had been provided, e.g., by the subcloning and sequencing techniques of Beguin et al., the presently claimed invention, capable of being expressed in plant cells, would still not have been obvious to one of ordinary skill in the art. The teaching of Carey et al. regarding heterologous promoters adds nothing to the rejection above of the presently claimed invention, particularly in plant cells. The teaching of Comai et al. is irrelevant for the reasons discussed below.

Attached is a copy of the executed Declaration under 37 C.F.R. §1.132 submitted with the amendment dated April 27, 1992, which was considered by the Examiner. It provides the analysis of an expert in the field distinguishing the present invention from the cited references. Reconsideration of all prior art rejections in view of this Declaration was requested, but the Examiner found the Declaration unpersuasive.

The Declaration clearly explains why one of ordinary skill in the art would not have been motivated to combine the cited references to arrive at the present invention.

The present invention provides vectors for the introduction of a completely exogenous gene into plant cells, which has not previously been accomplished. In particular, the analogy suggested by the Examiner between the Comai reference, which introduced an **additional** copy of a gene whose product is poisoned by a herbicide, does not apply in the present case, wherein a detoxifying enzyme is introduced into a plant which **never had** such a gene. Thus, the skilled worker

would not have been able to extrapolate the present invention from Comai et al., which was based upon a completely different concept. See the Declaration, page 2, item 1.

Also, in contrast with Comai, the present invention would result in the production of **products** not native to plant cells, and known in fact to be toxic. Therefore, again, a skilled worker would not have been able to predict if 2,4-D monooxygenase could be introduced into plants in order to protect them from the overall toxicity of 2,4-D. See the Declaration, page 3, item 2.

Therefore, the skilled worker would not be motivated to combine the references, and the present invention is not obvious in view of the reference. In re Laskowski, 10 U.S.P.Q.2d 1397 (C.A.F.C. 1989).

It is respectfully submitted that the Examiner has not given sufficient probative weight to the Declaration. When evidence is submitted in rebuttal of a prima facie case of obviousness, the decision maker must start over. The facts established by rebuttal evidence must be evaluated along with the facts on which the conclusion was reached, not against the conclusion itself. The earlier holding should not be considered as set in concrete. See, e.g., In re Eli Lilly & Co. 14 U.S.P.Q.2d 1741 (C.A.F.C. 1990); In re Rinehart, 189 U.S.P.Q. 143 (C.C.P.A. 1976). The question is not whether a skilled worker thought that **any** heterologous gene could be expressed in a plant per se, but, as the Declaration discusses, whether **that particular** expression product, the 2,4-D monooxygenase gene, could be expressed, which the Declarant stated was not predictable. It is therefore respectfully submitted that, in view of **all** of the evidence, taken together, the claims of the present invention were not obvious to a skilled worker at the time the invention was made.

Conclusion

In view of the above remarks, it is respectfully requested that the Board of Appeals **reverse** the rejections of the various claims and pass the application to issue.

Respectfully submitted,

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APPENDIX

17. Plasmids pVJH21, pGJS3, pKJS31, pKJS32, pKJSB330, pKJS(x)630 and pKJS32RH S', each a vector of claim 45.

18. Plasmids pTRJS'B435, pTJS'B436, pTJSS'035, pTJSS'036, pTJS'x535 and pTJS'x536, each a vector of claim 48.

23. A bacterial strain transformed with a vector of claim 48.

32. A transgenic microorganism or plant, comprising a microorganism or plant wherein a cell of said microorganism or plant is transformed with a vector of claim 48.

33. A transgenic plant containing a recombinant gene of claim 45.

35. A transgenic microorganism or plant comprising cells of a microorganism or plant transformed with a vector of claim 48.

42. A method of preparing a polypeptide having the biological activity of 2,4-D-oxygenase, comprising culturing a cell of claim 32.

43. A method of preparing a polypeptide having the biological activity of 2,4-D-oxygenase, comprising culturing a transgenic plant of claim 23.

45. A recombinant gene, comprising

a DNA sequence encoding a polypeptide having the biological activity of 2,4-D monooxygenase which is capable of being expressed in a plant, operably linked to

a heterologous promoter capable of promoting the expression in a plant of a structural gene operably linked thereto.

46. A recombinant gene of claim 45, wherein the DNA sequence is

the structural gene sequence of Figure 10, except that the initiation codon is ATG,

a DNA sequence differing therefrom by codon degeneracy, or

a DNA sequence hybridizable therewith or its complement, wherein the sequence or its complement codes for a polypeptide having said biological activity.

47. A recombinant gene of claim 45, wherein the structural gene sequence is derived from Alcaligenes eutrophus JMP134 plasmid pJP4, DSM 3840.

48. A recombinant vector comprising a recombinant gene of claim 45.

49. A recombinant vector comprising a recombinant gene of claim 46.

50. A recombinant vector comprising a recombinant gene of claim 47.

51. A transgenic plant of claim 33, wherein the exogenous DNA sequence encoding a polypeptide having the biological activity of 2,4-D monooxygenase which is capable of being expressed in a plant is operably incorporated into the genome of the host plant cell.

52. A method of claim 42, whereby the plant is protected against growth inhibition caused by treatment of the plant with a substituted phenoxyacetic acid.

53. A method of claim 52, wherein the substituted phenoxyacetic acid is 2,4-dichlorophenoxyacetic acid, 4-chlorophenoxyacetic acid or (2-methyl-4-chlorophenoxy)acetic acid.

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DECLARATION UNDER 37 C.F.R. §1.132

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

SIR:

I, Dr. Wolfgang R. Streber being duly warned, declare that:

I am a citizen of Germany, residing at Bartningallee 24, W-1000 Berlin 21, Germany.

I possess the degree of Dr. rer. nat. in Pharmacy, having studied at Ludwig-Maximilians-Universität in Munich.

Since March 1987 I have been employed as a scientist in the Agrochemicals Biotechnology Department of Schering Aktiengesellschaft, Berlin, Germany.

My expertise is demonstrated by my curriculum vitae, which is attached.

I have read and understood the references cited by the Examiner in the Office Action dated November 26, 1991 in the above-identified patent application. I have also read and understood the above-identified patent application.

A person having ordinary skill in the art of plant molecular biology would not find that these references render the claimed

invention obvious. This conclusion is based upon the following facts and observations:

1. Insofar as the inventors are aware, as of the August 29, 1986, priority date of this application, there had been no publication of any results regarding the expression of either a bacterial monooxygenase or any other comparable enzyme in plants. The only type of bacterial enzyme which had been expressed in the plants at the time were enzymes for which either an equivalent enzyme, e.g. EPSP-synthase (Comai et al.), or an essential factor, e.g. ATP for Neomycinphosphotransferase, or both were naturally present in the plants.

The Comai et al. reference therefore discloses the insertion of a very different bacterial enzyme with an endogenous homolog into a plant, as compared with the completely exogenous bacterial gene inserted in the present invention.
EPSP synthase is a protein which is **normally** present in the plant, is necessary for the viability of the plant and is poisoned by the herbicide glyphosate. Comai et al. merely inserted an **additional** copy of a gene coding for that necessary protein which was derived from a glyphosate-resistant bacterium.

In contrast, the present invention provides for the first time a 2,4-D monooxygenase gene and protein in plants, which do not normally possess such an activity. This enzyme posesses a highly unique biological activity. There was no way to predict from this reference, either alone or in combination with the other cited reference, whether:

a) the bacterial 2,4-D monooxygenase could be expressed inside eukaryotic cells, e.g., plant cells, and

b) even if it were, if the biological activity of the 2,4-D monooxygenase would be retained, and,

c) even if it were, if it would be retained at a level compatible with both

   i) the biological activity of herbicide-resistance and

   ii) the viability of the plant.

In particular, at the time the invention was made, there were no references disclosing the identification of the

biological activity of 2,4-D monooxygenase outside of living bacterial cells. In fact, the Amy et al. reference only shows the 2,4-D monooxygenase enzymatic activity in E. coli cells. It was not known whether there were additional factors present (or absent) inside bacterial cells the presence (or absence) of which were required for enzymatic activity.

2. 2,4-dichlorophenol, which is produced by 2,4-D monooxygenase from 2,4-dichlorophenoxy acetic acid (2,4-D), is known to be toxic to the respiration of living cells. At the time the invention was made, therefore, it would not have been obvious whether in the presence of a 2,4-D monooxygenase gene the plants would be protected from the toxicity of the reaction product 2,4-dichlorophenol, as well as from the toxicity of the 2,4-D itself, or if in fact, this reaction product would itself cause damage.

Therefore, in view of the differences in the enzymes, in particular the endogenous versus exogenous nature of the enzymes, the very different chemistry of the herbicides, the metabolic pathways affected, the toxicity of reaction products, etc., between the reference and the present invention, a skilled worker would not be able to predict anything from the cited references, particularly in view of Comai, with respect to the present invention.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the applciation or any patent issuing thereon.

3. April 1992

Date

W. Gruber

CURRICULUM VITAE

name:	Dr. Wolfgang R. Streber
date and place of birth:	24. Feb. 1958 in Munich, Germany

Education and Scientific Qualification:

1964 - 1977	school in Munich
Nov. 1977 - Oct. 1982	studies in pharmacy at the Ludwig-Maximilians-Universität (LMU) in Munich
Dec. 1982	awarded "Approbation" (degree) in pharmacy
Jan. 1983 - Feb. 1987	scientific work for doctoral dissertation in the group of Prof. Dr. M. H. Zenk at the Institute of Pharmaceutical Biology of the LMU about the bacterial metabolism of the herbicide 2,4-D
Feb. 1987	awarded doctorate in the faculty of Chemistry and Pharmacy (LMU)
since March 1987	employment as a scientist in the Agrochemicals Biotechnology Department of the Schering AG, Berlin

W. Streber